Diagnosis of deep-vein thrombosis and pulmonary embolism

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Diagnosis of Deep-Vein Thrombosis and Pulmonary Embolism: The New Guideline of the Dutch Institute for Health Care Improvement

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Summary

Reliable diagnosis of venous thrombosis or pulmonary embolism is crucial, as especially pulmonary embolism is a potentially fatal disorder. Recently the guideline of the Dutch institute for health care improvement (CBO), 'diagnosis, prevention and treatment of venous thromboembolism (VTE) and secondary prevention of arterial thrombosis' was published. The diagnostic algorithm in case of suspected VTE starts with a clinical decision rule according to Wells followed by a D-dimer test. These simple, non-invasive and cheap tests, exclude VTE in 25–30% of the patients with a suspected episode of VTE. With a dichotomized clinical decision rule, a 'likely' Wells score or an abnormal D-dimer concentration necessitates additional testing, like ultrasonography of the leg veins when deep-vein thrombosis is suspected, or multidetector computerized tomographic scanning in the case of suspected pulmonary embolism. These diagnostic algorithms considerably simplify the diagnosis of VTE.

Introduction

Diagnosing the presence of both deep-vein thrombosis (DVT) and pulmonary embolism is difficult. On one hand, anamnesis and physical examination are non-specific, as only 25–30% of the patients with clinical suspicion of venous thromboembolism (VTE) have this diagnosis. On the other hand, especially pulmonary embolism is a potentially fatal disorder that has a mortality rate, if untreated, of 26%. Adequate diagnostic tests to reliably exclude or confirm the presence of VTE is of utmost importance. In the present article we will summarize the recently published guideline of the Dutch institute for health care improvement (CBO) on the diagnosis of venous thrombosis and pulmonary embolism.

Diagnosis of DVT

In the last 10 years the use of D-dimer testing, combined with a clinical decision rule has been evaluated in many studies. The goal of these studies is the reliable exclusion of DVT, which will prevent unnecessary and expensive additional testing. Negative tests will withhold anticoagulant treatment in patients with a clinical suspicion of VTE.

Clinical decision rule

Based on anamnesis and physical examination, the probability of DVT can be calculated with the aid of a clinical decision rule (CDR). The CDR according to Wells has been validated best in prospective management studies. This rule is based on characteristics of anamnesis, physical examination and a possible alternative diagnosis and consists of nine items (Table 1) (1, 2).

Using the Wells score enables the stratification of patients in a low, intermediate or high probability of DVT. The negative predictive value of a low CDR is 96% and the negative likelihood ratio is 0.25 (3). The sensitivity of the test is too low to be used as the only diagnostic test to rule out DVT: additional testing, like D-dimer measurement or ultrasonography of the leg veins, is necessary. There are no management studies performed on the effectivity of CDR in patients with a suspicion of recurrent DVT. In addition, the interobserver variation of the Wells score is low ($\kappa = 0.85$) (1). Recently, Wells et al. have simplified their score into two categories, 'unlikely' with a score <2 and 'likely' when the score is 2 or higher (see next) (4).

Table 1: Clinical decision rule according to Wells with suspected deep-vein thrombosis (DVT)

	Score
Active cancer (patients receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bed-ridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anaesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	−2
High risk	≥3
Intermediate risk	1–2
Low risk	≤0
Likely	≥2
Unlikely	<2

D-dimer measurement

Thrombosis is associated with fibrinolysis of the clot, where under the influence of plasmin fibrin fragments are formed. One part of these fragments is called D-dimer. Several studies showed that a normal D-dimer level has a high negative predictive value when DVT is suspected. The current commercially available immunoassays for the determination of the D-dimer antigen include enzyme-linked immunosorbent assay (ELISA) and whole plasma agglutination measurements.

Several cohort studies in patients with clinical suspicion of DVT show that the sensitivity for the exclusion of DVT with D-dimer testing is high, while the specificity is low. The latter is caused by the fact that D-dimer levels tend to increase in non-thrombotic conditions, such as malignancy, infection, surgery and pregnancy, but also with increasing age. D-dimer testing should be used only in combination with the CDR or other diagnostic tests to exclude DVT. The sensitivity of the D-dimer test is too low to reliably exclude the presence of DVT.

Efficacy of CDR and D-dimer test in the diagnosis of DVT

The combination of a low probability and a normal D-dimer level is safe to withhold additional testing and anticoagulant treatment in patients with suspected DVT [recurrence rate 0.7%, 95% confidence interval (CI) 0.3–1.3%] (5, 6). These figures are mainly based on the combination of a normal D-dimer level and a low Wells score (≤0). One Dutch study evaluated the combination of a low and intermediate Wells score (<3) and a normal D-dimer level (Tinaquant) and found a low percentage of recurrent DVT of 0.6% (95% CI 0.1–3.1%) (7).

Using a dichotomized Wells score, an 'unlikely' Wells score <2 and a normal D-dimer test also resulted in a very high negative predictive value of 99.1% (95% CI 96.7–99.9%) and excluded no less than 39% of the patients with a clinical suspicion of DVT (4). A high CDR in combination with a normal D-dimer results in a very low negative predictive value to safely exclude DVT (4).

In summary, a combination using a simple CDR and D-dimer testing is effective to safely rule out DVT in clinically suspected patients. A diagnostic algorithm should always start with a CDR, and a D-dimer measurement should only be used when the CDR is lower than 2. When the CDR is likely, D-dimer testing is insufficiently reliable to exclude DVT. When either the CDR or D-dimer test is abnormal, additional diagnostic tests are required.

Ultrasonography

Ultrasonography is still the most commonly used non-invasive diagnostic method when DVT is suspected. The sensitivity is high (95%), especially for proximal DVT, with a specificity of 96%. The sensitivity for the detection of distal vein thrombosis seems considerably less compared with proximal DVT, with a sensitivity of around 73%. This is important as in about one-sixth of the cases extension of the thrombus to the proximal veins occurs.

Withholding anticoagulant treatment in the case of a negative result on compression ultasonography: combination of ultasonography and CDR or D-dimer

Usually, serial compression ultrasonography of the leg veins is performed to exclude the presence of DVT. The combination of a normal ultrasonography and a low CDR or a normal D-dimer is safe enough to exclude DVT and to withhold repeated ultrasonography (8). Even in the presence of an abnormal D-dimer test the probability of DVT is less than 1% with a normal ultrasonography, when CDR is low (9). Likewise, the combination of a normal D-dimer test results and a normal ultrasonography also reliably exclude DVT, irrespective of the CDR (9).

Consequently, it is safe to withhold anticoagulant treatment in patients with suspected DVT with a single normal compression ultrasonography in combination with either a low CDR or a normal D-dimer level.

Recurrent DVT

The diagnosis of recurrent DVT is often troublesome because of frequently present residual abnormalities of the deep-vein system. For example, ultrasonography of the leg veins is still abnormal in 50% of the patients 1 year after the first thrombotic event. A non-compressible venous

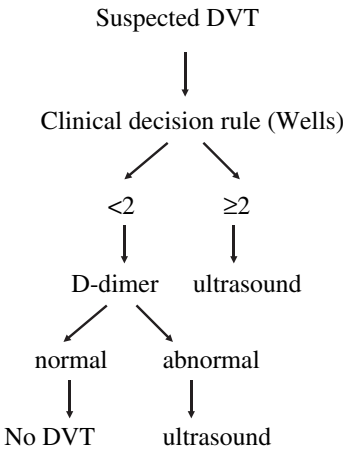
segment does not prove a new thrombosis; only in the presence of recent thrombus formation, a recurrent DVT can be diagnosed. A comparison with previous ultrasonography is therefore necessary. When a new non-compressible venous segment is found or if the thrombus has extended to more than 4 mm a recurrence is very likely (8, 10). When the diagnosis of a recurrent DVT cannot be excluded or established, flebography is necessary.

Flebography

Flebography remains the gold standard in the diagnosis of DVT. The experience with this diagnostic method however declines, because in daily clinical practice flebography is hardly ever performed anymore in The Netherlands and has nearly completely been replaced by ultrasonography. To our opinion, there are two remaining indications to perform a flebography: a clinically strong suspicion for DVT when compression ultrasonography is normal, and a suspicion of a recurrent DVT.

Diagnostic algorithm in the case of suspected DVT

In the presence of a clinical suspicion of DVT, a diagnostic algorithm should be started with a dichotomized CDR according to Wells. When this is score is lower than 2, a D-dimer level is measured. When this is normal, DVT is excluded. When the CDR is ≥2 or the D-dimer level is abnormal, additional compression ultrasonography is performed. When DVT is confirmed, anticoagulant treatment is started. If compression ultrasonography is normal, and either the D-dimer level is normal or the CDR is low, thrombosis can be excluded. When both CDR and D-dimer are high, despite a compression ultrasonography, the latter should be repeated after 5–7 days. This diagnostic algorithm is shown in Fig. 1.



■ **Fig. 1.** Diagnostic algorithm in patients with suspected deep-vein thrombosis.

■ **Table 2:** Clinical decision rule according to Wells with suspected pulmonary embolism

• Clinical signs of DVT	3.0 points
• Alternative diagnosis less likely than pulmonary embolism	3.0 points
• Heart rate > 100/min	1.5 points
• Recent surgery or immobilization	1.5 points
• Previous PE or DVT	1.5 points
• Hemoptysis	1.0 points
• Active malignancy	1.0 points
High risk	≥6
Intermediate risk	2–6
Low risk	<2
Likely	>4
Unlikely	≤4

Diagnosis of pulmonary embolism

Clinical decision rule

Also in case of suspected pulmonary embolism the CDR according to Wells has been extensively evaluated. It consists of seven items, based on clinical symptoms, physical examination and alternative diagnosis (Table 2) (10, 11).

Like in DVT, stratification of patients in a low, intermediate or high probability of pulmonary embolism using the Wells score is possible. The negative predictive value (NPV) of a low probability for pulmonary embolism is 97% (95% CI 72–99%) (12). Similar to DVT, the Wells score alone is insufficiently reliable to exclude pulmonary embolism: additional diagnostic tests, like D-dimer testing, ventilation/perfusion scan or multidetector computerized tomographic (CT) scan, is indicated.

Recently, the Wells score has been simplified into two categories, 'pulmonary embolism unlikely' when the score is 4 or less, and 'pulmonary embolism likely' when the score is higher than 4 (see next) (11). This CDR has been validated in a large Dutch prospective management study with consecutive patients with suspected pulmonary embolism (13). The dichotomized score may have a better interobserver variation compared with the three categories ($\kappa = 0.72$ vs. $\kappa=0.52$, respectively) (14). Also in patients with pulmonary embolism there is no management study performed on the efficacy of CDR in patients with a suspicion of a recurrent pulmonary embolism.

D-dimer test

The reliability of the D-dimer test for excluding pulmonary embolism is high. The risk of thromboembolic complications during 3 months follow-up was 0.21 (95% CI 0.0–0.8) for the quantitative tests (Vidas, Tinaquant) and 0.42 (95% CI 0.1–1.2) for whole blood agglutination (SimpliRED). When patients with pulmonary embolism and a normal D-dimer test were not treated with anticoagulants, no thromboembolic complications were seen during 3 months follow-up (0%, 95% CI 0–1.8%) (15, 16).

D-dimer testing has a very low specificity to be used as the sole diagnostic test to exclude the presence of pulmonary embolism.

Clinical effectiveness of the CDR and D-dimer test in patients with suspected pulmonary embolism

The combination of a low CDR and a normal D-dimer test result can safely rule out pulmonary embolism without the need for additional imaging (recurrence percentage 0.1–0.2%, 95% CI 0–0.8%) (17). A diagnostic algorithm using the dichotomized Wells score was evaluated in a large Dutch propspective management study in consecutive patients with clinically suspected pulmonary embolism (13). When patients who had a combination of a Wells score 'unlikely' and a normal D-dimer test results were not treated with anticoagulants, the 3 months recurrence rate of VTE was 0.5% (95% CI 0.2–1.1%), with an NPV of 99.5% (95% CI 98.9–99.8%). With this strategy, pulmonary embolism could be safely ruled out in 32% of the patients (prevalence of pulmonary embolism 20%). The results for outpatients and hospitalized patients were comparable [VTE incidence 0% (95% CI 0–6.7%) and 0.5% (95% CI: 0.2–1.2%), respectively].

In summary, the combination of a dichotomized Wells score ≤4 and a normal D-dimer test result is a safe strategy to rule out pulmonary embolism in patients with a clinical suspicion. This algorithm should start with a CDR, and D-dimer testing is only performed when the CDR according to Wells is lower or equal to 4. In case of a likely CDR, a normal D-dimer test result is not safe to rule out pulmonary embolism. In this case or when the D-dimer level is increased, additional imaging is necessary to safely exclude the presence of pulmonary embolism.

Computerized tomography

Computerized tomography has emerged as an important test in confirming or excluding pulmonary embolism. The NPV of the CT scan is 99.1%, with a low recurrence of VTE when CT scan excludes pulmonary embolism of 1.4%. These figures are mainly based on the single detector CT scan. The reliability of the multidetector CT-scan (MDCT) is higher than the single detector CT, probably because the MDCT scan detects more subsegmentel emboli. The previously mentioned Dutch management study assessed the effectiveness of the CT scan (mostly MDCT) in patients with clinically suspected pulmonary embolism who either had a likely probability or an abnormal D-dimer test (13). This CT scan excluded pulmonary embolism in 1505 patients, of whom 1436 were not treated with anticoagulants. The 3-month incidence of VTE was 1.3% (95% CI 0.7–2.0%) (13). Hence, a normal MDCT scan reliably excludes the presence of pulmonary embolism. Importantly, less than 1% of the MDCT scans were inconclusive.

Ventilation-perfusion scanning

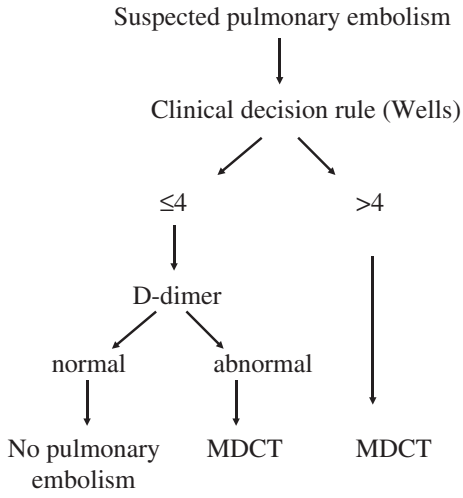
Perfusion scintigraphy reliably excludes the presence of pulmonary embolism. A high-probability ventilation/perfusion (V/Q) scanning has a sensitivity of about 88% for the confirmation of pulmonary embolism. The major problem with this imaging test is the high number of non-diagnostic V/Q scans of 30–70%. Additional testing with pulmonary angiography is necessary in these cases for a final conclusion. The number of non-diagnostic scans may be reduced when perfusion scintigraphy is only performed in patients who have a normal chest x-ray. The guideline of the British Thoracic Society proposes that perfusion scintigraphy can be applied as a first line diagnostic test, as long as the chest x-ray is normal, no significant symptomatic cardiovascular problems are present and there are standardized diagnostic criteria (18).

Pulmonary angiography

Pulmonary angiography still is the reference test for the detection of pulmonary embolism. An important drawback of this imaging technique is its invasiveness. Despite the low probability of complications, practitioners are reluctant to use it in clinical practice. A direct consequence is the decreasing expertise of radiologists.

Diagnosing suspected recurrent pulmonary embolism

It is often not possible to discriminate between old and new pulmonary emboli using imaging scans. Residual abnormalities on a perfusion- or CT-scan persist after a first episode of pulmonary embolism in more than half of the patients (19). Diagnosing a potential recurrent episode of pulmonary embolism may be better interpreted when after the first episode a control scan is performed to visualize the thrombus resolution.



■ **Fig. 2.** Diagnostic algorithm in patients with suspected pulmonary embolism.

Diagnostic algorithm in patients with clinically suspected pulmonary embolism (Fig. 2)

In patients with a clinically suspected episode of pulmonary embolism, a diagnostic algorithm first starts with a simple dichotomized clinical decision rule according to Wells. When the score is 4 or less and the D-dimer test result is normal, the presence of pulmonary embolism is excluded. When the CDR is >4 or the D-dimer test is abnormal, additional imaging with MDCT scanning is performed. This diagnostic management strategy is simple, safe and can be used in most patients with clinically suspected pulmonary embolism.

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